REMARKS/ARGUMENTS

I. Status of the Claims

Claims 19-46 are pending, with claims 33-46 being added herein.

II. The Present Amendment

No new matter has been added by the present amendments.

The new claims track the claims previously presented but focus on the raising of antibodies. The new claims to peptides of 15 or more contiguous amino acids of SEQ ID NO:2 are supported throughout the specification, including page 16, lines 10-16.

III. The Office Action

The Action rejects the claims on a number of grounds. Applicants amend in part and traverse all the rejections. For the reader's convenience, the rejections posed by the Action are considered below in the order in which they appear in the Action.

A. Rejections of Claims 19-32 Under 35 U.S.C. § 112, first paragraph as not enabled

The Action rejects some of the claims under 35 U.S.C. § 112, first paragraph as not enabled. Precisely which claims are rejected on this ground is not entirely clear, since the Action is unfortunately garbled on this important point (it reads "If remain rejected . . .); for purposes of this response it will be assumed that the rejection is of claims 19-32, as those were the claims rejected in the portion of the preceding Action to which the present Action refers. Applicants traverse the rejection.

1. The Rejection is inconsistent with the patents already issued on the same disclosure

Before turning to the specifics of the rejection, Applicants respectfully remind the Examiner that the current application is a divisional of 09/215,035, which application was

itself a divisional of application 08/776,271. These applications issued as U.S. Patent Nos. 6,153,430 and 6,083,502, respectively.

Claim 1 of the '502 patent, which issued on the grandparent application, reads:

"A method for specifically delivering an effector molecule to a tumor cell expressing mesothelin (SEQ ID NO: 2) or a portion thereof, said method comprising contacting said mesothelin or portion therein with a chimeric molecule comprise an effector molecule attached to a targeting molecule, wherein said targeting molecule specifically binds to a portion of mesothelin that is not recognized by monoclonal antibody K1, a monoclonal antibody secreted by a hybridoma deposited as ATCC Accession No. HB 10570, thereby delivering the effector molecule to the tumor cell".

Claim 26 of the '502 patent reads:

"A monoclonal antibody that specifically binds to a portion of mesothelin (SEQ ID NO: 2) that is not recognized by monoclonal antibody K1, a monoclonal antibody secreted by a hybridoma deposited as ATCC Accession No. 10570."

Claim 1 of the '430 patent, of which the present application is a divisional, reads:

"A recombinant nucleic acid comprising a nucleotide sequence encoding a polypeptide of SEQ ID NO:2."

Thus, based on the same disclosure, the Office has already issued claims to monoclonal antibodies which bind to a portion of SEQ ID NO:2, to methods of using chimeric molecules, such as immunotoxins, which comprise a molecule that targets cells expressing mesothelin, and to nucleic acids encoding SEQ ID NO:2. The patents are, of course, presumed to be enabled for that which is claimed.

The present rejection is based on the assertion that the specification does not enable the peptide encoded by the nucleic acid sequence claimed in the '430 patent or the portions of that peptide which would raise the antibodies claimed in the '502 patent. To the

extent the present rejection asserts that the specification does not enable peptides of SEQ ID NO:2 that would raise antibodies that bind to full-length SEQ ID NO:2, it cannot be reconciled with the '502 patent. To the extent the present rejection asserts that the present specification does not enable the full length mesothelin of SEQ ID NO:2 (as noted in the beginning, the rejection is garbled and it is not clear which claims are included), it cannot be reconciled with the '430 patent.

To sum up, the rejection is logically inconsistent with the '430 and '502 patents already issued by the Office on the same disclosure. Applicants submit that the Examiner must not only give full faith and credit to the conclusions of the Examiners who have previously examined the same specification, but also must respect the official position of the Office embodied in the '502 and the '430 patents that the disclosure enables, for example, the production of antibodies against portions of the mesothelin protein. Applicants respectfully maintain that the rejection must be reconsidered and withdrawn.

2. The rejection improperly imports methods into composition claims and then finds them not enabled for methods which are not recited in the claims

Since the rejection is a single lengthy paragraph, for ease of response, the discussion below breaks the rejection into sections and addresses the sections individually.

First, the Action correctly summarizes the Applicant's position that the claims currently under examination are drawn not to vaccines, but to isolated proteins and peptides, that the peptides and proteins can be used to raise antibodies, that only one utility is necessary for patentability and that the invention needs only to be enabled for that utility. Action, at page 2. The Action states, however, that:

> the claimed invention reads on anti-cancer vaccines and Applicant's previous amendments to the claims, to delete the term 'vaccine' does not alter that fact. Although no longer specifically recited in the claims, the vaccine limitation is inferred by the claim language because the claims read on the use of the claimed peptides and proteins as immunogens (which [read] specifically on *in vivo* administration) in patients with mesothelioma-or ovarian cancer-cells expressing

> mesothelin, given the understanding in the art that T-cells generated by vaccines will recognize, *ex vivo* the immunogen [used] to produce them *in vivo*, as well as the understanding in the art that administration of peptide vaccines [results] in not only a humoral but also a cellular immune response wherein both antibodies and T-cells are produced.

Action, at page 3. In other words, the Action's position is that, even though the claims are drawn only to proteins and peptides, they are not enabled because, the Action infers, they could also be used as vaccines.

Claims can, of course, be read as broadly as the claim language permits. But, here the Action reads into composition claims a method of use and then rejects the compositions as not enabled for the method of use it has read into them. Applicants respectfully submits this is not proper examination practice. The compositions claimed have a legitimate use, such as raising the antibodies to portions of SEQ ID NO:2 claimed in the '502 patent which issued on the grandparent application. It does not render the claims not enabled for that use to argue that they may also be used for another purpose. As the Applicants again respectfully remind the Examiner, only one utility is required for an invention. The corollary to this is that one must provide enablement for only that one utility to enable the claims.

Second, the Action continues:

> Further, given the clear teachings of the specification that the antibodies raised by the immunogens of the invention would be useful in inhibiting the spread or implantation of ovarian cancer cells in the peritoneal wall, given the teaching in the specification that the administration of peptides is well known for treatment of a variety of diseases, given the teaching that one of skill is able to extrapolate the information available for use of peptides to treat diseases associated with mesothelin peptides, given the specific teaching in the specification of vaccines comprising SEQ ID NO:2 or fragments thereof for the prevention of and inhibition of tumors, it is reasonable to infer from the claims as currently constituted that the claims read on anti-cancer vaccines for the treatment of mesothelioma-or

> ovarian cancer cells and that these limitations are encompassed by the claims and for the reasons of record, the claims are not enabled.

Action, at page 3 (emphasis added). Thus, once again, the Action fails to examine the proteins and peptides as actually claimed, but instead reads into the claims a method of use and then rejects the claims as not enabled for that method of use. As pointed out above, however, the claims need to be supported by only one utility and need only to be enabled for that one utility.

Third, the Action continues with the following statements:

> Finally, although Applicant suggest[s] that the claimed invention, SEQ ID NO:2 and variants thereof, is useful for the production of antibodies to be used for detecting the presence of mesothelin in a biological sample and for targeting cytotoxins to cells expressing mesothelin, given that the only useful function disclosed in the specification is apparently for the diagnosis and treatment of cancer, one would not know how to use the claimed invention if it were not used for the methods contemplated in the specification. If indeed there is no differential expression of SEQ ID NO:2 in cancer and normal tissues, one would reasonably wonder why one would make antibodies to target cytotoxins to normal tissues and what one would use information about the detection of SEQ ID NO:2 in a biological sample for except, perhaps, for experimental reasons. Further, Applicant appears to admit on the record that the specific function of SEQ ID NO:2 is unknown (see response, page 9, first full paragraph). Given this teaching, one would clearly not know how to use the claimed invention, or antibodies raised to said invention. The arguments have been considered but have not been found persuasive . . .

Action, at pages 4-5.

This part of the rejection rests on several fundamental errors. First, as an initial matter, Applicants note that it is immaterial that the specific function of the mesothelin antigen was unknown at the time of filing. For targeting toxins to cancer cells, for example, all that is needed is the knowledge that a particular cell marker is expressed on cells of the target cancer, but not on normal tissue that is essential to survival. See, e.g., page 1, lines 21-23.

Second, the Action incorrectly asserts that one of skill "would clearly not know how to use . . . antibodies raised to said invention." As noted in the first section above regarding this rejection, the Office has already issued a patent on methods of delivering effector cells using antibodies to portions of SEQ ID NO:2, based on the present disclosure. Thus, the Office has already conclusively determined that the present specification enables persons of skill both to raise antibodies against portions of SEQ ID NO:2 and to use the antibodies once they are raised.

Third, the Action speculates that there is no difference in the expression of mesothelin between normal and cancerous tissue. Even were this the case, the specification notes that an antigen can be present in substantial amounts on normal cells, if the normal cells are not part of an essential organ. See, page 1, lines 21-23. It is a commonplace of cancer therapy that the damage a cancer therapeutic may inflict on normal tissue has to be balanced against the benefit to the patient of attacking the cancer cells. And, in fact, a Phase 1 clinical trial has been conducted using an immunotoxin targeted by an anti-mesothelin antibody called "SS1" and found that the immunotoxin was well tolerated. (The anti-mesothelin antibody called "SS1" is the subject of co-pending application 09/979,539; its parent antibody, called "SS", is the subject of application number 09/581,345, now U.S. Patent No. 6,809,184.) A copy of the press release announcing the preliminary Phase I data released at the 2002 annual meeting of the American Society of Clinical Oncology is attached for the Examiner's convenience. As the Examiner will appreciate, the immunotoxin would not have proceeded into human clinical trials unless preclinical studies showed that it had efficacy against cancer that outweighed whatever damage the immunotoxin had to normal tissues.

Fourth, the Action's comments about the alleged problems with respect to vaccines clearly have no application to the new claims, which are directed only to peptides that generate antibodies.

In brief, then, the rejection improperly rests on importing method recitations into composition claims, and rejects the claims on bases that (1) are inconsistent with the official position of the Office, as embodied in the '502 and '430 patents issued on the same disclosure, and (2) are refuted by the entry of an immunotoxin targeted by an anti-mesothelin antibody into a clinical trial.

Reconsideration and withdrawal of the rejection in light of the above remarks is respectfully requested.

B. Rejection of claims 20-25, 27-32 as not enabled

The Action states that, if Applicant were able to overcome the rejection set forth in the preceding section, claims 20-25 and 27-32 would remain rejected under §112, first paragraph for the reasons set forth in section 5 of the August 2004 office action. According to the Action, the question is not whether the claims encompass non-working embodiments (which Applicants pointed out are permitted), but that the specification does not teach how to make the invention so it will function as broadly claimed. The Action asserts that the:

> specification does not point to critical regions of the polypeptide that must be conserved to produce the inferred anti-cancer vaccine, provides no guidance or information drawn to which regions of the claimed SEQ ID NO:2 are exposed on the surface of the undefined antigen, where the polypeptide is glycosylated, provides no information as to which epitopes are linear or 3-dimensional in the claimed variants of SEQ ID NO:2 wherein these variants are useful as the inferred anti-cancer vaccine.

Action, at pages 4-5. Applicants traverse.

This rejection is flawed, for several reasons. First, the rejection is grounded on the position that the claims are drawn to an inferred anti-cancer vaccine. As pointed in the preceding sections, however, this position requires improperly importing into the claims

recitations they do not contain and then rejecting them for failing to enable the imported recitations. Applicants respectfully request examination of the claims as presented.

Second, one of the rejection's contentions has already been shown to be factually in error. The Action asserts that the specification does not disclose where the protein is glycosylated. As pointed out, however, in the Amendment dated December 10, 2004 (hereafter referred to as the "December 2004 Amendment"), at page 16, however, Figure 2 of the specification shows the putative glycosylation positions, and the glycosylation of the protein is also specifically discussed in the specification, at page 9, lines 22-24. The present rejection apparently inadvertently overlooks this information. Thus, to the extent the rejection is premised on the alleged lack of information about glycosylation, it must be reconsidered and should be withdrawn.

Third, the statement that the specification contains no information on which epitopes are linear and which are conformational again is set forth in relation to the improperly imported, and non-existent, vaccine recitations. Antibodies recognizing linear portions of mesothelin are useful for immunological procedures, such as detecting the presence of mesothelin on electrophoresis gels or on blots. Further, Applicants pointed out in the December 2004 Amendment that an amino acid sequence itself contains the tertiary structure and would naturally form any conformational epitopes.

Finally, as pointed out above, the Office has already issued a patent on antibodies to portions of SEQ ID NO:2 based on the present disclosure. Thus, the Office has already conclusively determined that the present specification enables persons of skill, for example, both to raise antibodies against portions of SEQ ID NO:2 and to use the antibodies once they are raised. In sum, therefore, the rejection (i) rejects the claims for recitations they do not contain, (ii) is grounded on assumptions already shown to be incorrect and (iii) is contrary to the two patents the Office has already issued on the same disclosure. It should be withdrawn.

C. Rejection of Claims For Alleged Lack of Written Description

The Action maintains the rejection of claims 20-25 and 27-32 under §112, first paragraph. In brief, the Action rejects the arguments regarding the *Lilly* and *Enzo* cases made in

Applicants' Amendment dated December 10, 2004 (the "December 2004 Amendment"), stating that the courts have found that the fact pattern of these cases can be extrapolated to molecular products other than polynucleotides. The Action states:

> The issue raised here [is] that the specification as originally filed does not structurally describe a representative number of the genus claimed, does not describe structural features common to the members of the genus which features constitute a substantial portion of the genus, does not disclose functional characteristics coupled with a known or disclosed correlation between function and structure.

Action, at page 6. Applicants traverse.

It is not at all clear that the rejection has meaning in connection with the claims under examination. Whether or not a given peptide is immunogenic and will induce the generation of antibodies against it is not generally considered to be a "functional characteristic" of the peptide or one that requires a "disclosed correlation between function and structure." If this portion is applicable to the claims at all, which Applicants do not concede, it would appears that this rejection is again based on importing into the claims vaccine recitations they do not contain and then rejecting them over the imported, and non-existent, recitations.

To the extent the rejection is based on the alleged failure to describe a representative number of the genus claimed, the rejection appears to suggest that the specification is required to recite a series of peptide subsequences to meet the written description requirement. Applicants respectfully call the Examiner's attention to the recent decision of the Federal Circuit Court of Appeals in *Capon v. Eshhar*, No. 03-1480 (Fed. Cir. August 12, 2005), which overturned a decision by the Board of Patent Appeals and Interferences holding that neither specification in an interference between appellants Capon and Eshhar met the written description requirement. The *Capon* decision states:

> The "written description" requirement must be applied in the context of the particular invention and the state of the knowledge. The Board's rule that the

> nucleotide sequences of the chimeric genes must be fully presented, although the nucleotide sequences of the component DNA are known, is an inappropriate generalization. When the prior art includes the nucleotide information, precedent does not set a per se rule that the information must be determined afresh.
>
> . . .The "written description" requirement states that the patentee must describe the invention; it does not state that every invention must be described in the same way. As each field evolves, the balance also evolves between what is known and what is added by each inventive contribution.

Slip op., at page 15.

As noted in the Applicants' December 2004 Amendment, in *Lilly*, the applicant had not determined the sequence of cDNA for human insulin. The patent at issue contained a claims directed to a recombinant microorganism modified to contain a "nucleotide sequence having the structure of the reverse transcript of an mRNA of a [human] which encodes insulin." The specification in *Lilly* contained *no* sequence information. Instead, the specification provided only a general method of producing human insulin and a description of the amino acid sequences that the cDNA encodes. The Court held that this specification did not provide adequate written description of the claimed DNA, but rather a "mere wish or plan for obtaining" it.

The present specification sets forth much more than a mere wish or plan. It sets forth the entire amino acid sequence of mesothelin, including that of the 40 kD membrane bound portion remaining after proteolytic cleavage. The specification further refers to the raising of antibodies to subsequences of 10 or more amino acids of the mesothelin sequence. See, e.g., specification, at page 15, lines 1-7. This provides the information necessary for a practitioner to create subsequences of the protein, and to raise antibodies against the peptides that bind the parent protein.

What was known in the art was how to make peptides and how to raise antibodies to antigens. What was not known was the starting material, the sequence of mesothelin, necessary to make these peptides. The present specification provides that material by providing the sequence. Looking at the specification as a whole, therefore, the invention as claimed

adequately balances, in the words of *Capon*, what is known and what is added by the inventive contribution of the inventors.

Reconsideration and withdrawal of the rejection is respectfully requested.

D. Rejection of the Claims as Anticipated

The Action maintains the rejection of claims 19-25 and 27-32 and also rejects claim 26 under §102(b) as anticipated by Chang. Chang teaches a Western blot which the previous Action stated showed the presence of the purified 40 kD mesothelin protein; in their response to that Action, Applicants pointed out that a Western blot is designed to show the presence of the protein bound by the probing antibody but does not show other proteins that may be present but which are not bound by the antibody used.

The present Action states that this argument is not considered persuasive

> because the specification clearly teaches that the terms 'isolated,' 'purified,' or 'biologically pure' refer to material which is substantially or essentially free from components which normally accompany it as found in its native state. It is noted that the specification does not define the terms substantially or essentially free and one of ordinary skill would immediately understand that the protein isolated in a western blot is substantially and essentially free of components which normally accompany it as found in its native state given that the claimed protein is substantially or essentially free of nucleic acid molecules which normally accompany it in its native state.

Action, at pages 6-7, bridging paragraph. Applicants traverse.

Applicants agree that the Action correctly recites the specification's definition of the terms "isolated," "purified," and "biologically pure" as set forth at page 7, lines 9-12 of the specification. Applicants do not agree, however, that the Action is correct in its assertion that a protein identified by an antibody in a Western blot is "substantially or essentially free from

components which normally accompany it as found in its native state." As explained in the December 2004 Amendment, a Western blot shows the presence of the protein or proteins bound by the antibody used as a probe, but does not show the presence of any number of other proteins or other cellular components which are not bound by the antibody used to probe the blot. It is the ability of a Western blot to show the presence of the target protein in the midst of any number of other components that gives the technique its power.

The Action argues that the specification does not define the terms "substantially or essentially free" and that the practitioner would recognize that the protein would be free of "nucleic acid molecules which normally accompany it in its native state." Action, at page 7. The Action's argument, therefore, is that a protein on a Western blot would be considered by a person of skill "substantially free" of components which normally accompany it because it would be free of some components, even though it would be surrounded by any number of other components.

With respect, this argument is without merit. Applicants respectfully note that if the interest of the person of skill was to isolate a protein from only some of the components normally accompanying it, but not all, that person would be interested in isolating it from other proteins, which are far more likely than the nucleic acids hypothesized by the Action to interfere with the ability to determine the characteristics of the protein. Further, while the terms "substantially or essentially free" are not themselves defined, however, it is because they are expected to have the meaning that would normally be given them by persons of skill. Applicants respectfully maintain that phrase "substantially or essentially free" cannot be twisted to refer to a protein accompanied by any number of other proteins, as is true in a Western blot.

The rejection for anticipation relies on this incorrect statement of what a person of skill would understand from the term "isolated" with relation to the Western blot. Since the analysis is flawed, the rejection must be reconsidered. Reconsideration and withdrawal of the rejection is respectfully requested.

E. New Grounds of Rejection Under § 112, first paragraph

Claims 20-25 and 27-32 are rejected under § 112, first paragraph as allegedly not enabled. The new rejection extends from page 7 of the Action to page 25, and the first repeats a summary of contentions made in previous Actions (e.g., the remarks re the Bowie reference, on page 9 of the Action), and then, pages later, summarizes the Applicants' response to those contentions and sets forth the Examiner current assertions in response (e.g., the summary of Applicants' response regarding Bowie and her present assertions regarding Bowie, set forth in the Action at page 18). Applicants traverse the "new" rejection, which they maintain is adequately addressed in the December 2004 Amendment. To help clarify the record, however, certain of the Action's assertions will be more specifically addressed below.

1. Statements in the Action not supported by the references

Before turning to the specifics of the rejection, Applicants first call attention to an error that occurs in several places in the rejection. Applicants noted in the December 2004 Amendment that they could not find some of the statements allegedly made in the references cited by the Action. For example, at page 23 of the December 2004 Amendment, Applicants noted they could not find a statement alleged to appear in the Smith reference, and pages 25-26, bridging paragraph, and at page 27 of the Amendment, Applicants noted that they could not locate statements alleged to appear in the Boon reference.

Instead of showing that the references actually contain the statements which the Applicants noted they could not confirm the reference contained, however, the current Action regards the Applicants as having conceded the truth of the alleged statements by not denying them. In this regard, the Action states, at page 20, that "although Applicant asks for clarification as to where the information is found in the Smith article, Applicant does not argue that the statement in the action is not true," and, at page 24, with respect to Boon, states "although Applicant is unable to locate the cited passage, Applicant has not suggested that the information drawn to antigen presentation and abundance is not correct." With respect, this is not proper examination practice.

The Examiner is respectfully reminded that "to make a rejection, the examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention." MPEP § 2164.04. The Applicants pointed out to the Examiner that the references did not seem to contain the statements attributed to them, which is a respectful way of pointing out that the rejections appeared to be unsupported. The present Action does not show that the references in fact contain the statements ascribed to them by the previous Action. Instead, it attempts to reverse the burden by requiring the Applicants to respond to statements that the Examiner has not yet shown in fact exist.

With due respect, the Examiner's burden to establish a reasonable basis to question enablement cannot be met by citing a reference for a statement it does not in fact contain. To hold otherwise would be the same as saying that an examiner can simply make unsupported statements and force an applicant to rebut them, which would render the "reasonable basis" requirement of MPEP §2164.04 meaningless. It is therefore inappropriate for the Action to require the Applicant to deny a statement that a reference does not in fact contain. Applicants respectfully maintain that until the Examiner shows that the references actually contain the statements attributed to them, she has not yet placed the statements in issue and there is no burden on the Applicants to confirm or to refute them. Certainly, the rejections set forth in the Action cannot be supported by statements that do not in fact exist. The Examiner must point out specifically that the references contain the statements for which they are cited, withdraw the rejections that depend on those statements, or cite references that actually contain the statements. Under the MPEP, that burden is on the examiner, and until it is met, no proper enablement rejection can be raised. The rejection should be reconsidered, and withdrawn, on this basis alone.

2. The Bowie reference as support for the Action's contentions

At pages 9-10, the Action states that:

> One cannot extrapolate [from] the teaching of the specification to the scope of the claims because the claims as written are drawn to variants of SEQ ID NO:2 with 95 undefined alterations of the 628 amino acid residues of SEQ ID NO:2 as

> well as undefined variant which comprise 9 or 10 amino acid residues of SEQ ID NO:2 and neither the specification nor the art of record define which amino acid residues are critical to the raising of antibodies or which will be recognized by T-cells from patients with mesothelioma . . . As drawn to antibodies, Bowie, of record, teaches that an amino acid sequence encodes a message that determines the shape of a protein and determines the ability of said protein to fold into unique three-dimensional structures that allow[] them to function. Bowie further teaches that certain positions in the sequence are critical to the three dimensional structure function relationship and these regions can tolerate only conservative substitutions or no substitutions. . . . However, neither the specification nor the art of record provide teachings that provide information about the residues critical for epitopes required for the establishment of an immune response that will produce antibodies.

(Emphasis added). At page 18, the Action states:

> Applicant further argues that Bowie[] is not relevant to the instant rejection since this reference[] relate[s] to the biological activity of proteins. The argument has been considered but has not been found persuasive because Bowie is cited only to demonstrate the critical nexus between defined amino acid sequence and three dimensional structure. Examiner goes on to provide a nexus between three dimensional structure and antibody binding and generation. Applicant's argument appears to be moot.

To the contrary, the argument is not moot. Bowie is the Action's support for the contention that amino acids in a protein cannot be substituted or can only be substituted with conservative substitutions. This is in turn the basis for the Action's argument that variants of SEQ ID NO:2 are not enabled because, the Action asserts, the specification does not teach which residues are so critical that they cannot be substituted. But, as noted in Applicants' December 2004 Amendment, at pages 9-10, bridging paragraph, Bowie's comments on the effect of

substitutions in residues on the biological activity of a protein does not show there will be any effect on the immunogenicity of the protein. Bowie's teachings regarding the critical nature of some residue substitutions therefore do not provide support for there is a nexus between such substations and the characteristics of proteins as they are relevant to the claims under examination.

Applicants also respectfully observe that the Action does not even acknowledge, let alone address, their observation in the December 2004 Amendment that the Action

> "takes Bowie's statement out of context and thus fails to consider Bowie's teachings as a whole. Bowie's teaching as a whole is 'that proteins are surprisingly tolerant of amino acid substitutions . . . For example, . . . about one-half of all substitutions [made in a study substituting every position in the lac repressor] were phenotypically silent [citation omitted] At some positions, many different, nonconservative substitutions were allowed." Bowie, at page 1306, right column, first full paragraph (emphasis added). Thus, even in terms of maintaining a protein's biological activity, Bowie teaches that about one half of the residues can be changed without effect and that many nonconservative substitutions can be made."

Therefore, Bowie, cited by the Action against the claims, supports the prediction that many substitutions can be made in SEQ ID NO:2 or in fragments of SEQ ID NO:2 without affecting the ability of the protein or of fragments thereof to generate antibodies that bind the protein of SEQ ID NO:2 or of T-cells activated by endogenous mesothelin in a patient with a mesothelin-expressing cancer to recognize the protein or fragment.

3. The alleged lack of information in the specification

Applicants pointed out in the December 2004 Amendment that the specification in fact shows the four positions where the protein of SEQ ID NO:2 is glycosylated. *Id.*, at page 16. Rather than acknowledge this or modify the rejection based on this information, the present Action states as part of its argument that the specification does not provide adequate guidance on how to make and use the invention that the specification does not show where the protein is

glycosylated. For example, in response to the Applicants' point that variants or fragments of SEQ ID NO:2 could be tested for their ability to raise antibodies, the Action states:

> the specification provides no guidance or information drawn to which regions of the claimed SEQ ID NO:2 are exposed on the outside of the undefined antigen, where the polypeptide is glycosylated, [and] provides no information as to which residues are critical for the invention to function as broadly claimed.

Action, at page 16. This contention is repeated at page 17 in response to the Applicants' comment that this would not seem to relate to the raising of antibodies to linear epitopes. At page 19, the Action acknowledges that Applicants stated SEQ ID NO:2 has only four glycosylation points, but finds this not persuasive "because the issue raised here is not drawn only to the glycosylation sites but is drawn to the inadequacy of the teaching of the specification drawn to critical residues and regions of SEQ ID NO:2."

The Action is thus internally inconsistent within a single rejection. When necessary to augment its argument that the specification's teachings are inadequate, the rejection cites the alleged lack of information on glycosylation. When information on glycosylation is shown to exist, however, the Action simply states the issue is not about glycosylation at all, but about the alleged lack of teaching on critical residues (and, of course, the Action's assertions regarding critical residues is based on Bowie, which, as shown in the previous section, does not stand for the proposition for which it is cited). The Action cannot have it both ways.

Reconsideration is both warranted and requested.

4. The statement that the December 2004 Amendment's comments on Boon are "repugnant to the art"

On pages 22-23, bridging paragraph, the Action characterizes the Applicants' discussion of the Boon reference in the December 2004 Amendment as follows:

> Applicant argues that although Boon suggests that a cancer antigen may not be expressed on all cells of a cancer and therefore might not be therapeutically useful, it is useful to the practitioner and to the patient if disease progression is reduced by affording some

> response to those cells of the tumor that do express the antigen . . The argument has been considered but has not been found persuasive because Boon's teachings reflect the state of the art wherein it was known that the efficacy [of] antigen-specific therapy is dependent upon [the] abundance of antigen presented by the tumor. Applicants' suggestion that tumor progression can be reduced in the absence of sufficient abundance of the antigen target is repugnant to the art and goes against the teachings of those of skill.

With respect, the Action misstates the Applicants' position. The Applicants did not suggest "that tumor progression can be reduced in the absence of sufficient abundance of the antigen target." There has to be a target antigen present for any immunological approach targeting the antigen to be effective. For example, as noted in a preceding section of this Amendment, at least one clinical trial using an immunotoxin comprising a toxin fused to an anti-mesothelin antibody has been underway. Cells not expressing mesothelin would not be targeted by the immunotoxin.

What the Applicants were responding in the December 2004 Amendment was the contention that there might be variability between the amount of antigen present on cells in a tumor and some cells might not express the antigen. The point Applicants were making in response was that even if some cells of a tumor did not express the antigen, so long as some tumor cells do, the patient would be benefited by killing or inhibition of those cells that do express the antigen. In the case of an immunotoxin, for example, it can be expected that the overall growth of the tumor will be inhibited if at least some of its cells are being killed because they bear an antigen targeted by the immunotoxin. Thus, the Applicants maintained that the alleged variability of antigen expression on cancer cells, even if true, did not affect the enablement of the invention. Applicants again point out that the SS1-targeted immunotoxin discussed above would not have proceeded into human clinical trials if it had not exhibited efficacy in pre-clinical studies. Thus, the general concerns and speculation raised by the Action with respect to other types of cancer do not appear to apply to cancers that express mesothelin.

5. Alleged undue experimentation

The Action states that the specification provides no guidance or working examples which would provide guidance as to which amino acids or polypeptide fragments are critical to the production of antibodies which recognize SEQ ID NO:2 with a reasonable expectation of success. It further states that the specification does not identify which amino acids or polypeptide fragments are critical to production of antibodies that recognize full-length SEQ ID NO:2, and asserts that it would take undue experimentation to practice the invention. Action, at age 15. Applicants traverse.

Applicants respectfully remind the Examiner that whether or not experimentation is "undue" is determined under criteria that were articulated by the Federal Circuit in *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Those criteria are: (1) the breadth of the claims; (2) the nature of the invention; (3) the state of the prior art; (4) the level of one of ordinary skill; (5) the level of predictability in the art; (6) the amount of direction provided by the inventor; (7) the existence of working examples; and (8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. The presence or absence of working examples is only one of the eight factors *Wands* directs should be considered.

Lacking from the rejection is a consideration of the other seven factors, such as the level of skill in the art and the amount of experimentation that is routine. Applicants respectfully note that the persons of skill in this art are typically Ph.D. or M.D. level scientists. The level of skill is quite high, and the amount of guidance needed is correspondingly slight. Applicants respectfully note that , if persons of skill want to determine the immunogenic portions of a protein, they perform epitope mapping studies and use that information to determine which peptides will raise antibodies against the starting protein. While this amount of experimentation might be considerable, it is considered routine in the art. Applicants respectfully note that these statements are supported by the accompanying Declaration of Dr. Ira Pastan.

6. Loading dendritic cells with peptides

Applicants noted in the December 2004 Amendment that the peptides of the invention could be used to load dendritic cells, and presented references to show this technique

was well known in the art as of the priority date. The Action asserts that this argues limitations not in the claims, which it notes are not drawn to loaded dendritic cells. Action, at page 25.

The Action is correct that the claims are not drawn to loaded dendritic cells. They are drawn to proteins and peptides. As Applicants have already pointed out, however, only one utility is needed to enable an invention and, as the Applicants showed by appropriate references, loading dendritic cells with peptides was known in the art prior to the priority date of the application. Applicants maintain that this is yet another reason that the present claims are enabled.

The Action also contends that the Applicants have mischaracterized the court's statements in *In re Buchner*. Action, at pages 21-22, bridging paragraph. Applicants pointed to, *Buchner's* statement that the application need not teach, and preferably omits, that which is well known in the art, as support for the proposition that it was not necessary to teach antigen loading in the application to enable practitioners to make and use the invention in this way. The Action states that *Buchner* is drawn to the test of enablement, not to whether or not a specific embodiment is contemplated. *Id.* The Action does not present any argument, however, why a discussion of an embodiment of using an invention is any different from any other aspect of enablement, which is after all making and using the invention. Contrary to the Action's contention, therefore, Applicants respectfully maintain that the discussion in *Buchner* is in fact relevant to the present claims.

F. New Ground of Rejection of Claims for Lack of Written Description

Claims 20 and 23-26 are rejected under §112, first paragraph, for alleged lack of written description. Action, at page 25. The Action asserts that the recitation "at least 85% sequence identity to SEQ ID NO:2" has no clear support in the specification, and states that the specification, at page 6, lines 19-25, in fact teaches that the polypeptide "has substantial identity to another when it **has** (emphasis added) 85% sequence identity to a reference polypeptide." *Id.* The Action states that the modifier "at least " is drawn only to the 70% sequence identity. *Id.* Applicants traverse.

Applicants respectfully note that the Action's contention is based on the premise that the modifier "at least" applies only to the 70% percentage term. Here is the text of page 6 of the specification, at lines 21-24:

"comprises a sequence with at least 70% sequence identity to a reference sequence, or preferably 80%, or more preferably 85% sequence identity, or more preferably 90 identity . . . ".

The Action's thesis, then, is that the terms related to the first percentage stated, 70%, do not apply to the remaining statements of percentage identity. The text of the specification makes it clear, however, that the writer intended for the description of the first percentage of sequence identity to carry through to the others. The Examiner's attention is respectfully drawn to the second statement of percentage in the text, which reads in its entirety: "or preferably 80%. " Read in isolation, as the Action would have us do with respect to the 85% percentage recitation, the statement is meaningless, as it neither identifies the thing that is preferably 80%, nor of what the thing is 80%. The phrase gains meaning, however, when read in its context following the phrase "at least 70% sequence identity to a reference sequence". That is, read in context, it is clear both that the thing referred to preferably has at least 80% sequence identity to something, and that the something to which the thing against which sequence identity is being measured is a reference sequence. All of this understanding is, however, correctly read into the "or preferably 80%" because it is part of a series that starts "at least 70%."

The Action's contention emphasizes that the next phrase does not read "at least 85%" but states that the sequence "**has** 85% sequence identity". As noted, the emphasis is added by the Action. But the phrase in the specification does not say that the sequence **has** 85% sequence identity, as emphasized by the Action. It actually reads: "or more preferably 85% sequence identity." Once again, this phrase does not exist in isolation, but in a series that starts "at least 70%." Just as the description of the "at least 70% sequence identity" was intended to carry through to the otherwise meaningless "or preferably 80%", the "or more preferably 85% is part of a series and must be read in context. Applicants respectfully maintain that, while perhaps not expressed with the precision that might be desired in hindsight, the drafter was relying on

reading the first portion of the description, including the modifier "at least", into the following percentage phrases.

Applicants respectfully call the Examiner's attention to MPEP §2163.05 III, which instructs the Examining Corps to "take into account which ranges one of skill would consider inherently supported by the discussion in the original disclosure." In the case discussed in the MPEP at §2163.05 III, the addition of the new claim limitation "at least 35%" did not meet the description requirement because the phrase had no upper limit and caused the claim to read literally on embodiments outside a range taught in the specification. See, MPEP at page 2100-182. In contrast, the present specification discusses both proteins with "at least 70%" identity to SEQ ID NO:2 and the entire sequence of (that is, with 100% identity to,) SEQ ID NO:2. Sequences with between "at least 70%" identity to SEQ ID NO:2 on the one hand, and 100% identity to SEQ ID NO:2, on the other are plainly part of the invention as described. One of skill would therefore consider the claim recitation of "at least 85%" to be inherently supported by the disclosure. Even if the Action were otherwise correct, therefore, the claim limitation would not offend the description requirement.

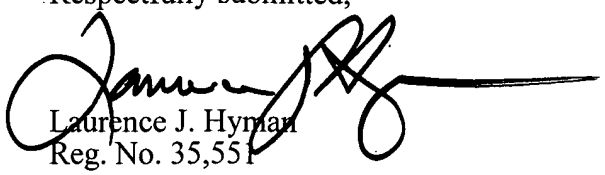
Reconsideration and withdrawal of the rejection are respectfully requested.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,



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NeoPharm Releases Preliminary Phase I Data For SS1(dsFv)-PE38 At ASCO Annual Meeting This W

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First Presentation Of Clinical Data On Novel Tumor Targeting Agent At Cancer Research Forum

LAKE FOREST, Ill., May 24 /PRNewswire-FirstCall/ -- NeoPharm, Inc. (Nasdaq: **NEOL**) today announced that the first preliminary Phase I human clinical data on the Company's novel tumor-targeting agent - SS1(dsFv)-PE38 - was unveiled at the 38th American Society of Clinical Oncology (ASCO) Annual Meeting held in Orlando, Fla. from May 18-21, 2002. This early Phase I scientific and pharmacokinetic data on SS1(dsFv)-PE38, currently being studied in advanced malignancies including mesothelioma and ovarian cancer, was released at ASCO this past week. One study was included as a scientific poster presentation and another study was included as a published abstract in the 2002 ASCO Program Proceedings. Data from these ongoing clinical studies provided early evidence of patient safety, tolerability and successful dose escalation. Copies of these NeoPharm abstracts are available online at: **http://www.asco.org .**

SS1(dsFv)-PE38 is the second agent to utilized NeoPharm's tumor targeting platform, in addition to IL13-PE38 for malignant glioma (brain cancer). SS1(dsFv)-PE38 uses the monoclonal antibody SS1(dsFv) to target receptors found in mesothelioma, ovarian cancer and other tumors, while IL13-PE38 uses the IL13 protein to target receptors on brain and kidney tumors. Malignant mesothelioma - a devastating form of lung cancer - is diagnosed in approximately 2,200 cases annually within the United States, with patient median survival typically around five months. Approximately 27,000 new cases of ovarian cancer are diagnosed in the U.S. every year. Unfortunately, therapeutic options remain inadequate - resulting in an annual mortality rate of 15,000 patients with advanced or recurrent disease.

NeoPharm has licensed worldwide rights to each of these tumor targeting compounds from the National Cancer Institute (SS1(dsFv)-PE38) and the U.S. Food and Drug Administration (IL13-PE38). Both agents have received orphan drug designation from the FDA (SS1(dsFv)-PE38 for mesothelioma and ovarian cancer, and IL13-PE38 for malignant glioma).

The Mechanism of SS1(dsFv)-PE38 as an Anti-Mesothelin Immunotoxin

Mesothelin is a cell surface antigen that is over-expressed on most mesotheliomas, ovarian cancers and other malignancies. SS1(dsFv)-PE38 - an anti-mesothelin immunotoxin - works by deploying a two-step mode of action. One component of the molecule carries the tumor-cell identifier - SS1(dsFv), which selectively seeks out, recognizes and binds to cancerous tumor cells. The other component then selectively delivers a potent bacterial cytotoxic agent - called PE38 derived from Pseudomonas bacterium - to destroy tumor cells while sparing healthy surrounding cells.

According to James Hussey, President and Chief Executive Officer of NeoPharm: "The early data we've seen thus far on SS1(dsFv)-PE38 supports our belief that we're heading in the right direction with our tumor targeting platform. Both SS1(dsFv)-PE38 and IL13-PE38 are designed to serve unmet medical needs in critically ill patient populations who suffer from rapidly progressing, terminal forms of cancer. There are few therapeutic options to treat these malignancies. Our goal is to develop breakthrough anticancer agents, using novel delivery technology, to transform progress into promise

for these individuals."

Phase I SS1(dsFv)-PE38 Study Objectives: Toxicity, Maximum Tolerated Dose, Pharmacokinetics

Both NeoPharm abstracts released at ASCO evaluated SS1(dsFv)-PE38 in advanced malignancies. The poster (Poster Board A14 - Abstract #113) presented early data on alternate-day infusion of SS1(dsFv)-PE38 in patients with advanced malignancy of selected mesothelin-positive histology and the absence of anti-toxin neutralizing antibodies in their serum. This Phase I trial was designed to determine the toxicities, maximum tolerated dose (MTD) and pharmacokinetics of SS1-PE38 by intravenous (IV) infusion QOD for six doses in patients. In the study, patients received SS1-PE38 intravenously bolus for six doses, on Monday, Wednesday and Friday for two weeks. The treatment doses tested to date were 8 ug/kg/dose (3 pts.); 12 ug/kg/dose (3 pts.); 18 ug/kg/dose (3 pts.); and 25 ug/kg/dose (3 pts.). Patients developed antibody to SS1(dsFv)-PE38 after one course and Day 10 drug levels were decreased, suggesting that the neutralizing antibody had appeared, a finding observed with systemic administration of other tumor targeting toxins. Two patients had transient minor response and two additional patients showed a decrease in malignant ascites. The conclusions of this Phase I study indicated that SS1-PE38 was well tolerated in patients with advanced mesothelin-expressing solid tumors, and the neutralizing antibody has limited repeat dosing. The MTD has not been reached, and patient accrual continues.

In the second, Phase I continuous infusion study (Abstract #1896), patients received SS1(dsFv)-PE38 via continuous intravenous infusion for 10 days. The dosing regimen was 4 ug/kg/dose (3 pts.); 8 ug/kg/dose (3 pts.); and 12 ug/kg/dose (3 pts.). All patients except one developed antibody to the drug after a single treatment course and, as a result, no patients received a second infusion. Patient enrollment at 12 ug/kg/dose continues in order to define the MTD and assess effect on mesothelin-expressing malignancies.

Strategic Collaborations Advance New Research to Validate Proof of Concept

"We're encouraged by these preliminary findings in SS1(dsFv)-PE38 studies to date," commented Raffit Hassan, MD, Assistant Professor of Medicine of the University of Oklahoma Health Sciences Center, study investigator and main author of the SS1(dsFv)-PE38 poster presentation. "Our initial research provides further 'proof of concept' that SS1(dsFv)-PE38 can be delivered as a tumor targeting agent through intravenous administration," he continued. Dr. Hassan's research has been supported in part by a Career Development Award from ASCO.

NeoPharm's collaborations with additional leading cancer centers provided the first clinical data on SS1(dsFv), an agent discovered in the laboratory of Ira Pastan, MD, Chief, Laboratory of Molecular Biology, National Cancer Institute (NCI) - a known leader in the field. Other study investigators on the SS1(dsFv)-PE38 research poster included Robert J. Kreitman (NCI); Manish Gupta (University of Oklahoma Health Sciences Center) and Mark Willingham (Wake-Forest University, Winston-Salem, NC). Dr. Kreitman, as well as David Squires and Diana O'Hagan - both from NCI's Laboratory of Molecular Biology - were authors of the published SS1(dsFv)-PE38 abstract. Collaborators from NeoPharm on both the poster and published abstract included: Lewis Strauss, M.D, Vice President of Clinical Development and Christina Fleming, Ph.D. Director, Clinical and Medical Communications.

Additional Phase I Data on IL13-PE38 - NeoPharm's Other Tumor Targeting Agent - Released at ASCO

NeoPharm and its collaborators are continuing to advance the preliminary Phase I clinical studies for SS1(dsFv)-PE38 in advanced malignancies. In addition to SS1(dsFv)-PE38, new preliminary data from NeoPharm's tumor targeting platform - IL13-PE38 for treatment of malignant glioma - was released at ASCO. Three IL13-PE38 abstracts (#1841, #2087 and #2088) were published in the 2002 ASCO Program Proceedings - two revealing Phase I/II data on intratumoral infusion of IL13-PE38 in malignant glioma (Abstracts #2087, #2088), and one studying the clinical and pharmacokinetic effects of systemic administration of IL13-PE38 in advanced renal cell carcinoma (Abstract #1841).

Both intratumoral infusion studies in glioma have provided additional data indicating that IL13-PE38 may have potential as a safe and effective treatment for resectable as well as recurrent malignant glioma supratentorial tumors. These preliminary clinical data substantiate other Phase I data for IL13-PE38 recently presented at the CNS Section on Tumors Fifth Biennial Satellite Symposium, held in conjunction with the American Association of Neurological Surgeons (AANS) Annual Meeting in Chicago. The first Phase I human clinical trial data on IL13-PE38 in malignant glioma was presented in November 2001 at the Sixth Annual Meeting of the World Federation of Neuro-Oncology/ Society for Neuro-Oncology (SNO) in Washington, DC. NeoPharm is hopeful of advancing IL13-PE38 into Phase II/III trials by year-end. The Company also has plans to evaluate the drug's effects in malignant glioma in a pediatric patient population.

Nine Scientific Abstracts on NeoPharm's Entire Phase I Portfolio at ASCO Annual Meeting

This year, ASCO accepted all nine (9) NeoPharm scientific abstracts submitted for release at the Annual Meeting. These abstracts highlighted NeoPharm's entire Phase I portfolio of cancer treatment agents across the Company's proprietary NeoLipid(TM) Electrostatic Liposome Encapsulation and Tumor-Targeting platforms. Preliminary data were published in Volume 21 of the peer-reviewed 2002 ASCO Program Proceedings on NeoPharm's tumor targeting agents - two studies on SS1(dsFv)-PE38 [Abstract #s 113, 1896] and three studies on IL13-PE38 [Abstract #s 1841, 2087, 2088] - as well as NeoPharm's NeoLipid compounds including Liposome-Encapsulated c-raf Antisense Oligodeoxynucleotide (LErafAON) [Abstract #s 107, 1845] and Liposomal Encapsulated Mitoxantrone (LEM) [Abstract # 2147]. In addition to the published abstracts, NeoPharm presented preliminary Phase I studies on two of its compounds as scientific posters. These posters included early human clinical data on LErafAON [Poster Board #A8, Abstract #107] and SS1(dsFv)-PE38 [Poster Board #A14, Abstract #113].

The published and poster abstracts revealed encouraging preliminary data from NeoPharm's ongoing clinical studies with SS1(dsFv)-PE38 for systemic use; IL13-PE38 using intratumoral administration; and LErafAON and LEM for intravenous use. These abstracts revealed early evidence of patient safety, tolerability and successful dose escalation. ASCO also accepted for publication in the 2002 ASCO Program Proceedings (Volume 21) an abstract on NeoPharm's novel approaches to integrated Phase I/II dose escalation and neoadjuvant trial design - Abstract #2156 - which is currently being implemented for studies of potent cytotoxins administered as pre-operative intratumoral infusion. The abstract outlined innovative steps undertaken to identify minimum effective dose (MED) below the maximum tolerated dose (MTD). Copies of all NeoPharm abstracts are available online at: **http://www.asco.org** .

About NeoPharm

NeoPharm, Inc., based in Lake Forest, IL, is a publicly traded

biopharmaceutical company dedicated to the research, discovery and commercialization of new and innovative cancer drugs for therapeutic applications. The Company has a broad portfolio of compounds in various stages of development.

Additional information about NeoPharm and recent news releases can be obtained by visiting NeoPharm's Website at: **http://www.neophrm.com** . For copi the scientific abstracts mentioned in this press release, visit the ASCO Website (**http://www.asco.org**) or contact Larry Kenyon, NeoPharm, at 847.295.8

This press release contains "forward-looking statements" within the meaning of Section 27A of the Securities Act of 1933 and Section 21E of the Securities Exchange Act of 1934. Such statements include, but are not limited to, any statements relating to the Company's drug development program and any other statements that are not historical facts. Such statements involve risks and uncertainties, including, but not limited to, those risks and uncertainties relating to difficulties or delays in development, testing, regulatory approval, production and marketing of the Companies' drug candidates, unexpected adverse side effects or inadequate therapeutic efficacy of the Companies' drug candidates that could slow or prevent products coming to market, the uncertainty of patent protection for the Company's intellectual property or trade secrets and other risks detailed from time to time in filings the Company makes with Securities and Exchange Commission including their annual reports of Form 10-K and their quarterly reports on Forms 10-Q. Such statements are based on management's current expectations, but actual results may differ materially due to various factors, including those risks and uncertainties mentioned or referred to in this press release.

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